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Effects of the inverse alpha agonist doxazosin in allergic rhinitis

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Running head: Doxazosin in allergic rhinitis

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Abstract**Background:**

We examined the paradoxical hypothesis that the alpha receptor inverse agonist doxazosin might produce beneficial effects in allergic rhinitis.

Objectives:

To evaluate single and chronic dosing effects of doxazosin on nasal airflow and symptoms in allergic rhinitis.

Methods:

15 patients randomized to receive 3-5 weeks of oral doxazosin 4mg daily or placebo in cross-over fashion. Measurements were made at baseline and after first and last doses.

Results:

There was a fall in peak nasal inspiratory flow (PNIF) between baseline vs first dose of doxazosin: mean difference -19 L/min (95%CI -35 to -2) $P=0.03$, with recovery between first and last doses: 21 L/min (95%CI 7 to 34) $P=0.006$. Nasal visual analogue scale (VAS) and blockage scores were worse between baseline vs first dose of doxazosin: mean difference VAS -10 mm (95%CI -18 to -2) $p=0.02$, blockage -0.7 (95%CI -1.3 to -0.1) $p=0.02$; with recovery between first and last doses: VAS 15mm (95%CI 4 to 25) $p=0.009$, blockage 1.1 (95%CI 0.5 to 1.6) $p=0.001$. The oxymetazoline dose response for PNIF was blunted after single vs chronic dosing: mean difference -17 L/min (95%CI -30 to -4) $P=0.01$. Heart rate and diastolic blood pressure showed the same pattern. There was a significant difference between doxazosin and placebo for nasal blockage score and heart rate after single but not chronic dosing.

Conclusions:

There was a disconnect between single and chronic dosing effects of doxazosin for nasal symptoms, oxymetazoline response and cardiovascular outcomes, in turn suggesting alpha-1 receptor up-regulation .

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Keywords:

Allergic rhinitis, peak nasal inspiratory flow, alpha receptor antagonist, alpha receptor inverse agonist, doxazosin

Abbreviations:

ANOVA:	analysis of variance
95%CI:	95% confidence interval
DRC:	dose response curve
MID:	minimal important difference
Nasal NO:	nasal nitric oxide
PNIF:	peak nasal inspiratory flow
RQLQ:	rhino-conjunctivitis quality of life questionnaire
SEM:	standard error of mean
TNS4:	total nasal symptom score
T _{1/2} :	elimination half life
VAS:	nasal global visual analog scale score

Introduction

Current management guidelines for allergic rhinitis advocate the use of nasal corticosteroids and anti-histamines as first line therapy [1]. However despite such treatment there is an unmet need with many patients remaining symptomatic in terms of persistent nasal blockage, especially in those patients who have reduced airway patency due to inferior turbinate hypertrophy.

Alpha-receptor agonists such as oxymetazoline are available without prescription and provide effective acute decongestant relief, mediated by direct vasoconstriction of the nasal sinusoids and by vasoconstriction of afferent arterioles and arterio-venous shunts, leading to a reduction in blood flow to the sinusoids. However their repeated use is associated with a rapid tachyphylaxis of response due alpha-receptor down regulation and G-protein uncoupling, resulting in desensitization of response [2]. In addition to tachyphylaxis of the vasoconstrictor response there is also an associated increase in nasal airway hyper-reactivity and rebound worsening of nasal congestion, resulting in the so called syndrome of rhinitis medicamentosa [3]. Hence alpha-agonists are only recommended for decongestant use on a temporary short term basis in patients with allergic rhinitis, for example to aide nasal breathing during an acute viral episode.

In healthy volunteers, after repeated dosing with oxymetazoline, there is a reduction in nasal airway patency as reflected by a fall peak nasal inspiratory flow (PNIF) along with a rightward shift in the dose response curve (DRC) to oxymetazoline due to alpha-receptor down regulation [4]. A single dose of the alpha-1 antagonist prazosin produces an acute fall in PNIF as well as blunting of the PNIF dose-response curve (DRC) to oxymetazoline [4]. This suggests that the predominant vasomotor response

in the human nose is mediated alpha-1 receptors in keeping with previous in vitro studies [5].

In healthy volunteers the dorsal hand vein vasoconstrictor DRC to the alpha-1 agonist phenylephrine was shifted by seven fold to the right after the first dose of the alpha-1 antagonist terazosin compared to baseline, but after 4 weeks of terazosin the dose response to phenylephrine returned back to baseline, in turn indicating that alpha-1 receptor up regulation occurs during chronic dosing [6, 7].

These data have in turn led to a novel paradoxical pharmacological hypothesis [8], namely that chronic dosing with a selective alpha-1 receptor antagonist doxazosin might be beneficial in allergic rhinitis by producing alpha-1 receptor up regulation and associated resensitisation of alpha receptor mediated responsiveness. Doxazosin exhibits strong inverse agonist activity [9] at the alpha-1 receptor and may therefore be able to inhibit constitutive unliganded receptor activity in addition to its antagonist activity by inhibiting the receptor when activated by ligand. The presence of inverse agonist activity also appears to be related to the propensity for inducing up regulation of alpha-1 receptors [10].

Such a paradigm shift in thinking from agonist to antagonist (or inverse agonist) has already been seen in heart failure, where chronic exposure beta-agonists was found to be unhelpful due to beta-receptor down-regulation and associated desensitization of cardiac inotropic response. The use of beta-receptor antagonists in heart failure was contra-indicated due an acute worsening in cardiac function after first dose exposure. It was not until clinical trials looked past this initial deterioration that the improvements in cardiac function, morbidity and mortality were seen in heart failure during chronic dosing with beta-blockers [11, 12]. Interestingly a similar paradoxical scenario has also been recently postulated in asthma [13], whereby chronic

exposure to long acting beta-2 agonists may in certain genetically susceptible individuals cause worsening of disease control [14] and associated airway hyper-reactivity [15]. There have been conflicting results in asthma with beta-blockers which exhibit inverse agonist activity in that chronic dosing open label nadolol improved airway hyper-reactivity [16], while placebo controlled trials with propranolol have failed to show any benefits [17, 18].

The underlying hypothesis is that one might perhaps expect opposite beneficial effects on the nasal vasculature upon repeated exposure to the inverse agonist doxazosin as compared to the agonist oxymetazoline . Hence the purpose of present proof of concept study was to evaluate the putative disconnect between single and chronic dosing effects of alpha-1 receptor blockade with doxazosin on nasal airflow and symptoms in allergic rhinitis, as a consequence of inverse agonist activity and associated alpha-1 receptor up-regulation. We also measured the response to oxymetazoline as a surrogate to follow alpha-1 receptor regulation. In addition we wanted to assess what might happen in the presence of an acute inflammatory nasal insult induced by a bolus dose of histamine after stopping doxazosin and how this might influence the subsequent recovery in response to oxymetazoline. As we have previously shown that topical corticosteroid may produce alpha-1 receptor up-regulation and augment the response to oxymetazoline [4], we therefore decided to obviate this potential confounding effect by stopping any nasal corticosteroid therapy for the duration of the study. Anti-histamines were also stopped for the duration so as not to interfere with the histamine challenges. Hence we enrolled patients with mild allergic rhinitis who might be able to manage without such treatments for the duration of the study, instead using nasal cromoglycate spray on demand.

Materials and Methods

We enrolled patients with a physician based diagnosis of mild allergic rhinitis [19] who had at least one positive skin prick test to a panel of common aeroallergens. Patients with a history of seasonal allergic rhinitis were evaluated out with the pollen season. Rigid nasal endoscopy was performed at screening to exclude those patients who had evidence of a deviated nasal septum (>50%), obstructive inferior turbinate hypertrophy, obstructive adenoidal hypertrophy or nasal polyposis. Patients were required to exhibit at least a 20 L/min and 20% reversibility in PNIF during a DRC to oxymetazoline using a diluent (baseline) followed by cumulative doses of 25ug, 50ug and 100ug (sum of both nostrils) at 15 minute intervals, as previously described [4].

Patients were also required to be able to withhold nasal steroids and anti-histamines for the duration of the study. Patients with a systolic blood pressure less than 100mm Hg were excluded along with any other vasodilators which might interact with doxazosin to adversely lower blood pressure. Informed written consent was obtained from all patients and the Tayside medical ethics committee approved the protocol (Ethics 13/ES/0010, Clinical Trials.gov NCT01946035, EudraCT 2012-005035-85).

A randomized double blind placebo controlled cross-over design was employed (Figure 1) where patients received either prolonged release Doxazosin (Cardozin XL, Arrow Generics Ltd, Stevenage ,UK) 4mg once daily in the evening or identical (over-encapsulated) placebo (Royal Free Hospital, London UK) for 3-5 weeks. There was a 1-3 week run-in and washout period in between randomized treatments, the rationale being that a minimum duration of 1 week would exceed a period of five elimination half lives ($t_{1/2} = 9$ hours) for doxazosin [20]. The prolonged release

formulation was chosen to improve tolerability in terms of the propensity for hypotension in association with a smoother pharmacokinetic profile.

Measurements were made at baseline after run-in and washout and at 12 hours after the first and last doses of each randomized treatment including PNIF and symptoms, along with a DRC to oxymetazoline (25ug, 50ug and 100ug cumulative dose). The construction of the oxymetazoline DRC at 12 hours after dosing was chosen to coincide with the mid point of the daily dosing interval when using the prolonged release formulation, to ensure maximal receptor occupancy.

At baseline and at each of the single and chronic dosing visits the following were also recorded: total nasal symptom score (TNS4) comprising blockage, sneezing, itching and discharge - ranging from 0 (absence of symptoms) to 3 (severe) within each domain (i.e. a total score of 0-12), global nasal visual analog scale (VAS) symptom score ranging from 0 (absence of symptoms) to 100mm (very severe symptoms) [21], supine/erect heart rate and blood pressure. Juniper rhino-conjunctivitis quality of life score (mini RQLQ) [22] and nasal nitric oxide (NO) [23] were measured at baseline and after chronic dosing.

In addition at 36 hours after the last dose patients attended for a further separate visit where they were given a bolus dose of nasal histamine (6.4mg) after initial diluent followed by a subsequent oxymetazoline DRC during recovery post challenge (25ug,50ug,100ug cumulative dose). Throughout the study patients also recorded domiciliary diary cards for PNIF. Patients were permitted to use nasal Cromoglycate spray 2% on demand during the entire study having stopped their usual treatment with either nasal steroids or anti-histamines.

PNIF measurements were taken as the best of three measures from an In-check flow meter (Clement Clarke International Ltd, Harlow, England). Technique was

evaluated to ensure a seated posture, horizontal positioning of the meter, correct restoration of the reading to zero, a closed mouth, and an adequate mask seal while making a maximal nasal inspiration. Nasal NO was measured using a chemiluminescence analyzer (NIOX; Aerocrine AB, Stockholm, Sweden) under standard conditions using the standard aspiration technique recommended by the American Thoracic Society guidelines [24] using a unilateral nasal olive, breath-holding, and velum closure at a flow rate of 50 ml/s.

Statistical Analysis

The study was powered at 80% to detect a minimal important difference of 5l/min [25] (within subject SD 7 L/min) in the primary end point of PNIF with an alpha error of 0.05 (two tailed). Baseline values after run-in and washout were compared paired Students T tests. An overall repeated measures analysis of variance (ANOVA) was applied to evaluate visit based effects for PNIF and other secondary outcomes, followed by paired Students T tests to compare different time points. An overall repeated measures ANOVA was used to compare serial time points for the overall oxymetazoline DRC's.

Results

15 patients completed per protocol comprising 7 males, mean (SEM) age: 37 (3) years, PNIF: 135 (12) L/min, VAS 19 (5) mm, nasal blockage score 0.9 (0.3), TNS4 score 3.2 (0.8), with a mean of three positive skin prick tests for each individual. All patients were taking anti-histamines, either regular or on demand, two were taking nasal steroids, and one was taking leukotriene receptor antagonist. None were taking alpha-agonists. The participant flow is shown in Figure 2.

Visit based nasal outcomes:

Data for all visit based outcomes in response to randomized treatments are summarized in Table 1. Baseline values after run-in and washout prior to randomized treatments were not significantly different for any of the outcomes. There was a significant overall effect ($P=0.01$) on PNIF comparing serial time points. There was a fall in PNIF between baseline and the first dose of doxazosin: mean difference -19 L/min (95%CI -35 to -2) $P=0.03$, along with recovery back to baseline between the first and last doses: mean difference 21 L/min (95%CI 7 to 34) $P=0.006$ (Figure 3). Differences in PNIF between placebo and doxazosin were not significant after single: mean difference 18 L/min (95%CI -1 to 37) $P=0.06$, or chronic dosing: mean difference 12 L/min (95%CI -6 to 30) $P=0.18$.

There was a significant overall effect ($P=0.04$) on global nasal VAS score comparing serial time points. The VAS score (0-100mm) showed worsening between baseline and the first dose of doxazosin: mean difference -10mm (95%CI -18 to -2) $p=0.02$, with recovery back to baseline between first and last doses: mean difference 15 mm (95%CI 4 to 25) $p=0.009$ (Figure 3). The VAS score was not significantly different

after the first dose of placebo versus doxazosin: mean difference -9 mm (95%CI -18 to 1) P=0.07.

The nasal blockage score (0-3) also showed the same pattern in terms of a significant overall effect (P=0.001) and also comparing baseline and first dose with doxazosin: mean difference -0.7 (95%CI -1.3 to -0.1) p=0.02 and between first and last doses: mean difference 1.1 (95%CI 0.5 to 1.6) p=0.001 (Figure 3). There was also a difference in blockage score between placebo and doxazosin after the first dose: mean difference -0.7 (95% CI -1.4 to -0.02) p=0.04.

The overall TNS4 score (0-12) was only significant comparing the first and last doses of doxazosin: mean difference 1.5 (95%CI 0.1 to 3.0) p=0.04, and there was no difference between placebo and doxazosin. No difference was observed in the other TNS4 domains including the rhinorrhea score.

Mini RQLQ scores were not different comparing values between baseline and chronic dosing with doxazosin: (1.59 verses 1.29) mean difference -0.30 (95%CI -0.70 to 0.10) P=0.13, or with placebo: (1.67 verses 1.58) mean difference:-0.09 (95%CI -0.72 to 0.54) P=0.76. Chronic dosing values for placebo and doxazosin were also not different.

There were no differences in geometric mean nasal NO values between chronic dosing with doxazosin (376 ppb) verses respective baseline (295ppb): geometric mean fold difference 1.28 (95%CI 0.90 to 1.82) P=0.16, or between chronic dosing with placebo (304 ppb) versus respective baseline (318ppb): geometric mean fold difference 0.96 (95%CI 0.77 to 1.19) P=0.68.

Oxymetazoline DRC:

The oxymetazoline DRC for PNIF was relatively blunted after single compared to chronic dosing with doxazosin: mean difference -17 L/min (95%CI -30 to -4) $P=0.01$ (Figure 4), but no such difference in oxymetazoline DRC was seen after single vs chronic dosing with placebo: mean difference -4 L/min (95%CI -16 to 7) $P=0.41$. The oxymetazoline DRC was not different when comparing placebo and doxazosin after chronic dosing: mean difference 1 L/min (95%CI -10 to 13) $P=0.83$.

The magnitude of the acute fall in PNIF in response to histamine challenge was not altered comparing placebo vs doxazosin after chronic dosing: mean difference 6 L/min (95%CI -7 to 18) $P=0.31$ (Figure 5). The subsequent PNIF recovery with oxymetazoline post histamine challenge was also no different comparing placebo vs doxazosin: mean difference 4 L/min (95%CI -16 to 25) $P=0.66$.

Visit based cardiovascular outcomes:

There was a significant overall effect on supine ($P=0.002$) and erect ($P=0.001$) heart rate as well as on erect diastolic blood pressure ($P=0.04$) comparing serial time points. Heart rate was increased from baseline after the first dose of doxazosin: supine mean difference 9 beats/min (95%CI 3 to 14) $P=0.003$, erect mean difference: 12 beats/min (95%CI 5 to 20) $P=0.004$, and recovered back to baseline between the first and the last doses: supine mean difference -9 beats/min (95%CI -15 to -2) $P=0.01$, erect mean difference -13 beats/min (95%CI -23 to -3) $P=0.01$.

There was a significant difference in the first dose effect between doxazosin and placebo for supine heart rate: mean difference 6 beats /min (95%CI 1 to 11) $P=0.03$ and for erect rate: mean difference 12 beats/min (95%CI 5 to 19) $P=0.004$. Erect diastolic blood pressure was lowered after the first dose of doxazosin compared to

baseline: mean difference -6 mmHg (95%CI -11 to -1) P=0.04, along with recovery between first and last doses: mean difference: 5mmHg (95%CI 1- to 10) P=0.02.

Domiciliary PNIF:

There were no differences in mean domiciliary PNIF values between pre-treatment baseline (run-in/washout) and the last week of doxazosin: (139 verses 142 L/min) mean difference -1L/min (95% CI -13 to 11) P=0.82, or between pre and post values for placebo: (139 verses 143 L/min) mean difference -4 L/min (95%CI -23 to 16) P=0.70. Chronic dosing values for placebo and doxazosin were also not significantly different.

Discussion

The results of this proof of concept study showed that alpha-blockade resulted in worsening of nasal airflow (as PNIF) and symptoms (as global VAS and nasal blockage scores) after the single but not chronic dosing with doxazosin. Thus, after the last dose PNIF, VAS and blockage scores had all returned back to baseline. We observed a significant difference between doxazosin and placebo for nasal blockage score and heart rate after single but not chronic dosing.

The worsening in nasal airflow and symptoms after initial exposure is due to acute vasodilatation consequent upon blockade of the prevailing sympathetic vasomotor tone in the nasal sinusoids. The difference between single and repeated dosing is most likely explained by adaptive up regulation of alpha-1 receptors in the nasal vasculature [7], although we did not measure nasal alpha receptor density in the present study. The same disconnect between single and chronic dosing was also seen with cardiovascular responses. It is worth mentioning that there were no differences when comparing baselines between visits after run-in and washout, confirming there were no carryover effects between the randomized treatment arms. This is to be expected since the duration of washout of at least one week (i.e. 168 hours) greatly exceeds a period of five elimination half-lives for doxazosin (i.e. 45 hours) [20].

It is pertinent to distinguish between what may be statistically significant and clinical relevant differences. Hence the observed difference between single and chronic dosing in VAS score of 15mm is less than the minimal important difference (MID) of 23mm [26], while the corresponding difference in overall TNS4 score of 1.5 exceeds the MID of 0.55 [25], and for PNIF the difference of 21 L/min exceeds the MID of 5 L/min [25].

We also observed that the acute decongestant response to oxymetazoline was relatively blunted after the first compared to the last dose with doxazosin. This infers that resensitization of alpha-1 receptors occurred at 12 hours after the last dose of doxazosin, which would correspond to a period of maximal receptor occupancy at steady-state with the modified release formulation of doxazosin. In the dorsal hand vein model the phenylephrine response returned back to baseline after 4 weeks of treatment with terazosin having been initially blunted after the first dose [6]. Indeed the oxymetazoline DRC after the last dose of doxazosin was not different from placebo, suggesting that full recovery of alpha-1 receptors had occurred. Serial measurement of nasal alpha receptor binding density would however be required to confirm this assumption.

The same disconnect seen for nasal airflow and symptoms was also observed when comparing single and chronic dosing effects upon heart rate and on erect diastolic blood pressure. The increase in heart rate after the first dose of doxazosin is due to reflex vagal withdrawal following peripheral vasodilatation. However no patients reported any symptoms attributable to postural hypotension which could reflect use of the prolonged release formulation given to relatively young subjects.

We also performed a bolus histamine challenge to try and mimic the scenario where patients might be exposed to an acute nasal insult such as an allergen, virus or chemical. This showed that the acute fall in PNIF in response to histamine as well as the subsequent oxymetazoline recovery were no different at 36 hours after the last dose of doxazosin as compared to placebo. We performed the challenge at a time when there should be diminished residual receptor occupancy, since 36 hours equates to a period of four elimination half-lives for doxazosin [20]. It seems unlikely that at 36 hours there is any persistent alpha-1 receptor up-regulation given that

there was no evidence of any rebound effect on histamine PNIF fall or altered oxymetazoline recovery after stopping doxazosin. In the dorsal hand vein model there was found to be no difference in response to phenylephrine at 72 hours after stopping terazosin as compared to baseline [6].

We chose doxazosin not only for its availability as a well tolerated modified release preparation but also because of its strong inverse agonist activity [9]. As with beta-blockers such as carvedilol which exhibit inverse activity in heart failure [12], we considered that this pharmacological property of doxazosin might also prove to be beneficial in allergic rhinitis. It might also be interesting to evaluate the effects of topical administration of doxazosin which would achieve much higher local concentrations in nasal mucosa, although such a formulation is not available.

The clinical implication of these findings is that at least in the medium term over 3-5 weeks the use of oral alpha blockade does not result in any therapeutic benefit for patients with mild allergic rhinitis in terms of nasal airway patency or symptoms. For such patients who are taking concomitant alpha blockers for the indications of hypertension or prostatic hypertrophy, there appears to be no cogent rationale for stopping treatment.

We stopped nasal steroids for the duration of the study so as to obviate any potential confounding effect due to alpha receptor up-regulation [4]. Hence we were only able to include patients with mild allergic rhinitis who could manage without nasal steroids and anti-histamines for the duration of the study. We appreciate that we may not be able to reliably extrapolate our results to what might happen in the presence of concomitant nasal steroids in more severe patients.

We appreciate the limitations of our proof of concept study in mild patients with allergic rhinitis. First, we did not have a control group which might comprise either healthy volunteers or perhaps patients with non allergic rhinitis.

Second, we can not extrapolate our results to what might happen in more severe patients taking concomitant intranasal corticosteroids. Finally we did not measure nasal alpha receptor binding density and therefore can only postulate about serial receptor regulation in response to doxazosin. Nonetheless the nasal and cardiovascular outcomes all going in the same direction would tend to suggest that tachyphylaxis had occurred as a consequence of receptor up-regulation.

In conclusion, we observed a disconnect between single and chronic dosing effects of doxazosin for nasal airflow, symptoms, oxymetazoline response and cardiovascular outcomes, in keeping with up regulation of alpha-1 receptors. Further long term studies with doxazosin may be warranted perhaps in patients with non allergic rhinitis, or in more severe patients with allergic rhinitis taking intranasal corticosteroids ,to explore the therapeutic potential of its inverse agonist activity in terms of effects on nasal airflow, symptoms and quality of life.

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Conflict of Interest Statement

Dr. Manoharan has received money from Chiesi to attend meetings.

Mrs Morrison has nothing to disclose.

Dr. Lipworth reports grants and personal fees from Chiesi, personal fees from Boehringer Ingelheim, grants and personal fees from Meda, grants and personal fees from Teva, grants from Janssen, grants from AstraZeneca, grants from Roche

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Table 1. Data for visit based outcomes according to randomized treatments

	Placebo			Doxazosin		
	Baseline	Single dose	Chronic dose	Baseline	Single dose	Chronic dose
PNIF (L min ⁻¹)	157(16)	155(16)	170(17)	156(15)	137(14)*	158(14)†
VAS (mm)	23(6)	25(6)	20(4)	24(5)	34(5)*	19(4)†
Nasal blockage score (0-3)	1.3(0.3)	1.4(0.3)	1.3(0.2)	1.4(0.2)	2.1(0.3)* #	1.1(0.2)†
Overall TNS4 (0-12)	3.6(0.8)	3.5(0.7)	3.2(0.4)	4.1(0.8)	4.3(0.8)	2.8(0.5)†
Supine heart rate (bpm)	73(4)	74(3)	71(3)	72(3)	80(4)* #	72(4)†
Erect heart rate (bpm)	82(4)	84(3)	82(3)	84(3)	96(5)* #	83(3)†
Supine systolic BP (mmHg)	131(3)	135(4)	133(5)	131(4)	133(3)	132(3)
Erect systolic BP (mmHg)	130(3)	129(4)	133(4)	132(4)	125(3)	130(4)
Supine diastolic BP (mmHg)	79(3)	78(3)	79(3)	79(3)	78(2)	80(3)
Erect diastolic BP (mmHg)	81(2)	80(3)	84(3)	85(3)	79(2)*	84(3)†

Data are presented as means (SEM)

*denotes a significant difference between baseline and single dosing for the effect of doxazosin

†denotes a significant difference between single and chronic dosing for the effect of doxazosin

denotes significant difference after single dosing between placebo and doxazosin

Figure Legends

Figure 1

Flow chart for study visits. A placebo controlled randomized cross-over design was used. Baseline measures after run-in and washout were performed at Visits 2/6, while single dose effects were measured at visits 3/7 and chronic dose effects at visits 4/8 (at 12 hours post dose). At each of these visits an oxymetazoline dose response curve was also performed. At visits 5/9 after the last dose, a bolus histamine challenge was performed along with subsequent recovery in response oxymetazoline (at 36 hours post dose).

Figure 2

Consort diagram showing participant flow

Figure 3

Effects of single and chronic dosing with doxazosin or placebo on (a) peak nasal inspiratory flow (PNIF L/min), (b) nasal blockage score (0-3 units), (c) global visual analog scale (VAS) score (0-100 mm). Asterisk denotes a significant difference between baseline and single dosing, while cross denotes a significant difference between single and chronic dosing for the effect of doxazosin. Hash sign denotes a significant difference in blockage score between placebo and doxazosin after the first dose. Values are shown as means and SEM.

Figure 4

Cumulative oxymetazoline (OXY) dose response curve (DRC) showing PNIF response after single and chronic doses of (a) placebo and (b) doxazosin. Asterisk denotes a significant difference in terms of relative blunting of overall oxymetazoline PNIF dose response comparing first versus last doses of doxazosin. There was no significant difference in dose response between first and last doses of placebo. Values are shown as means and SEM.

Figure 5

Effect of a bolus histamine challenge and subsequent recovery on PNIF in response to oxymetazoline at 36 hours after the last dose of doxazosin or placebo. There was no significant difference between doxazosin and placebo comparing the PNIF fall in response to histamine or the subsequent oxymetazoline recovery. Values are shown as means and SEM.